REMARKS

Interview

Applicants thank Examiner Travers for his time and attention in the interview held on December 12, 2003. The arguments presented at the interview will be summarized in this response and additional arguments and evidence will be presented.

Status of the Claims

Claims 1-25 are pending in this application. No claims have been canceled, added or amended. Applicants submit the following arguments in support of the allowability of the claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejects claims 1-25 as not enabled by the specification. Applicants traverse the rejection and respectfully request the withdrawal thereof.

No *Prima Facie* Lack of Enablement

Applicants submit that the Examiner has failed to meet the burden of presenting a *prima facie* case of lack of enablement. See *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). *Wright*, citing *In re Marzocchi*, 169 USPQ 367, 369 *(CCPA 1971)* states

> *When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.*

The Examiner has failed to meet this initial burden.

In the Office Action, the Examiner states that the present invention cannot be practiced without undue experimentation. The Examiner sets forth the *Wands/Forman* factors and attempts to give reasons why the present invention would require undue experimentation. The Examiner merely states, without rationale, that the field of art is unpredictable and that the genus of NK_1 antagonists and $5HT_3$ antagonists is vast and would necessitate an exhaustive search. The Examiner also states that the specification fails to set forth useful NK_1 and $5HT_3$ antagonists and that one of ordinary skill could not determine useful NK_1 and $5HT_3$ antagonists without undue experimentation. The Examiner also states that the number of working examples is not sufficient.

Applicants submit that the Examiner's attempt to analyze the disclosure with the *Wands* factors falls short of establishing a

prima facie case of lack of enablement. As such, Applicants request that the rejection be withdrawn.

The *Wands* Factors

Applicants submit that pursuant to *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), the test for enablement is whether one of ordinary skill in the art would have to engage in undue experimentation to practice the invention. In *Wands*, the Federal Circuit found that the claims were enabled even where one of ordinary skill in the art would have to engage in production and screening of numerous monoclonal antibodies to practice the invention.

The present case is similar to the case in *Wands*. In *Wands*, the invention was directed to a method of detecting particular antigens using high affinity monoclonal antibodies of the IgM isotype. The central issue of enablement was whether the screening method (method of determining a high affinity IgM isotype antibody) was unpredictable and unreliable. The specification in *Wands* disclosed a method of producing monoclonal antibodies (by using hybridomas) against the specific antigen. The specification also disclosed working examples. Such is also the case in the present specification.

Intrinsic Evidence of Enablement

The present specification discloses NK_1 receptor antagonists by chemical name, structure and function. The specification also discloses $5HT_3$ antagonists by name and function. The specification discloses that the combination is useful in a method of treating a mammal suffering from or susceptible to emesis.

NK_1 Receptor Antagonists

Numerous compounds are identified as NK_1 receptor antagonists at pages 2 to 19 of the specification. Suitable compounds are described in various patents, which are mentioned in the specification. Preferred NK_1 receptor antagonists are compounds of formula I. The screening method for determining if compounds are NK_1 receptor antagonists is disclosed at page 25, lines 16 to 23 of the specification. An *in vitro* assay using rabbit cerebral cortex membranes is outlined in Dam et al., Peptides (7) pages 855-864 (1986) to determine if a compound has the ability to displace ^3H-substance P in the rabbit cortex. This article is cited in the specification. An additional screening assay is also disclosed that uses the method disclosed in Brown et al., Tachykinin Antagonists, Hakanson, R. and Sundler, F. (Eds.) Elsevier:Amsterdam, pages 305 to 312 (1985) using the rabbit

thoracic aorta. This article is also cited in the specification. Moreover, an example of the preparation of the compound of formula I is disclosed at page 28, line 26 to page 31.

Applicants submit that just as Wands disclosed a screening assay, so does the present specification. Likewise, both Wands and the present specification disclose examples of how to make or produce the product (compound or antibody) to be screened.

Furthermore, the level of predictability in the Wands invention and the level of predictability in the present invention are relatively the same. In *Wands*, the court recognized that the method for screening monoclonal antibodies was well known in 1980. Likewise, the methods for screening for NK_1 receptor antagonists were well known several years before the earliest priority date of 1991. See the cited articles dated 1985 and 1986.

$5HT_3$ Antagonists

With respect to the claimed $5HT_3$ antagonists, the specification describes three different $5HT_3$ antagonists, namely ondansetron, granisetron and metoclopramide. These compounds were already known in the art prior to the filing date of the present application (see page 22, line 8 of the specification).

Conclusion

As is apparent from the above discussion, the claimed invention can utilize known compounds and therefore the state of the relevant art (for enablement purposes) was well developed. In fact, it is submitted that the state of the relevant art in the present situation was more developed than the art in the *Wands* case. Therefore, the claims in the present application are fully enabled by the specification, in light of the state of the art.

As such, Applicants submit that when applying the holding in *Wands* to the present case, this rejection should be withdrawn as the present invention can be practiced without undue experimentation.

Extrinsic Evidence of Enablement

Applicants also submit the attached journal articles in support of the arguments that the specification enables one of ordinary skill in the art to practice the presently claimed invention. At the time the present application was filed one of ordinary skill would know how to determine or screen for tachykinin antagonists, specifically NK_1 receptor antagonists, and $5HT_3$ antagonists agents, as supported by the following extrinsic evidence submitted herewith.

NK_1 Receptor Antagonists

As recited above, Brown et al. and Dam et al. disclose screening assays for NK_1 receptor antagonists. Also, *Dutta, A. S. Chapter: "Tachykinin Receptors". Comprehensive Medicinal Chemistry,* vol. 3, pp 1001 - 1022. Ed. Emmett, J.C. (1990) discloses that tachykinin receptors in a variety of tissues had been classified as NK_1, NK_2 or NK_3 using both selective agonists and antagonists. Therefore at this time it would have been possible for someone of ordinary skill to determine whether a compound was a NK_1 antagonist.

Copies of the above cited references are attached hereto. Clearly, methods of detecting NK_1 receptor antagonists were known to persons of skill in the art at the time the invention was made, particularly since Brown et al and Dam et al. are cited in the specification. Therefore, one of ordinary skill in the art can determine with little effort if a particular compound is an NK_1 receptor antagonist.

$5HT_3$ Antagonists

Ondansetron, trade name ZOFRAN®, was well known at the time the present invention was made. Ondansetron was approved by the FDA by January 4, 1991 (before Applicants' earliest British

application) as evidenced by the listing in the FDA's Orange Book. Following ondansetron, several other $5HT_3$ antagonists have been developed and marketed, including but not limited to granisetron, palonosetron, dolasetron and alosetron. Ondansetron was also described in The Physician's Desk Reference as a known $5HT_3$ antagonist in 1992 at copy is attached hereto.

Granisetron, palonosetron, dolasetron and alosetron are all also cited in the FDA's Orange Book. Copies of the Orange Book listings for these drugs are attached. Moreover, U.S. patents describing each on these compounds as a $5HT_3$ antagonist was either published or filed before 1992. Copies of each are attached. U.S. Patent 4,886,808 describes the chemical compound known as granisetron, which was known as possessing 5-HT antagonist activity. See column 9, line 54. U.S. Patent 5,202,333 entitled "Tricyclic 5-HT_3 Receptor Antagonists" was filed on May 22, 1991. The '333 patent describes the 5HT3 antagonist compound known as palonosetron. U.S. Patent 4,906,755 the chemical compound known as dolasetron is described as a $5HT_3$ receptor antagonist. The '755 patent also describes both in vitro and in vivo assays for determining if a compound is a $5HT_3$ receptor antagonist. See column 5, lines 63 to column 7, line 18. Alosetron is described in U.S. Patent 5,360,800,

filed August 7, 1991 as a $5HT_3$ receptor antagonist. See for example the Abstract and column 4, lines 25 to 33.

Research on $5HT_3$ antagonists dates back to the 1970's when $5HT_3$ antagonists were commonly known as serotonin M antagonists. Please see Bradley et al., Proposal for the Classification and Nomenclature of Functional Receptors for 5-Hydroxytryptamine, *Neuropharmacology*, Vol. 25, No. 6, pp. 563-576 (1986) attached hereto. Bradley et al. discloses that serotonin M antagonists were renamed $5HT_3$ antagonist. Several articles were published in the 1970's describing methods of determining serotonin M antagonists activity ($5HT_3$ antagonists). Please see J. Fozard, et al., Blockade of Neuronal Tryptamine Receptors by Metoclopramide, *European Journal of Pharmacology*, vol. 49, pp. 109-112 (1978) and J. Fozard, et al., Blockade of Serotonin Receptors on Autonomic Neurones by (-) Cocaine and Some Related Compounds, *European Journal of Pharmacology*, vol. 59, pp. 195-210 (1979). Fozard (1979) discloses a guinea pig ileum assay for detecting septonin antagonists. Fozard (1978) discloses a rabbit heart assay for detecting M serotonin antagonists($5HT_3$ antagonists).

Functional assays, such as rat vagus nerve, rat superior cervical ganglion and guinea pig ileum assays, are used to

identify $5HT_3$ antagonists. These methods are all described in Bulter, A. et al., "Pharmacological Properties of GR 38032F, a novel antagonist at 5-HT_3 receptors", *British Journal of Pharmacology*, 94(2), pp. 397-412 (1988). A copy is attached.

A number of potent $5HT_3$ antagonists had been identified by 1992. The compounds primarily studied during this time were ondansetron, granisetron and tropisetron. Therefore, there was no mystery on determining a $5HT_3$ antagonist compound at the time of Applicants' first British application.

Moreover, GB 2152049A, published July 31, 1985, discloses serotonin M antagonists. See page 9, line 3, which describes the assay for detecting compounds, which exhibit serotonin M receptor antagonist activity as "standard tests." The "standard tests" are described from page 9, line 4 to line 49. Also, GB 2100259A, published 1982, discloses 5HT antagonists and a screening assay to determine if a compound is a 5HT antagonists, where the pA_2 value of the compound can be tested. See page 3, lines 17-24. This assay not only detects 5HT antagonists, but also determines the most potent compounds.

Formulations, modes of administration and doses were also all known to those of ordinary skill in the art at the time the present invention was made. Both GB 2100259A and GB 2152049A

disclose formulations, administration and dose along with biological and/or clinical data on serotonin M antagonists. Also, U.S. Patent 4,695,578 discloses how to make, formulate and administer ondansetron, which is a known $5HT_3$ antagonists.

Conclusion

As such, Applicants submit that at the time the present application was filed, one of ordinary skill in the art would know how to determine if a tachykinin compound was an NK_1 receptor antagonist or if a compound was a $5HT_3$ antagonist. Only routine screening would be necessary to determine if a compound is suitable for use in the present invention. Thus, Applicants respectfully request that this rejection be withdrawn.

Finally, it is noted that claims of almost identical scope to many of the claims in the present case were granted by the USPTO in U. S. Patent 5,576,317 (the '317 patent). It is submitted that the disclosure of the present application, in all respects relevant to the enablement issue raised in the Office Action, is as good as the disclosure of the '317 patent. Therefore, the Examiner should allow the claims in the present application so that an interference can be declared between the present application and the '317 patent.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner also rejects claims 1-25 as being indefinite because criteria for determining whether compounds are NK_1 antagonists or $5HT_3$ antagonists are not set forth in the specification. Applicants traverse the rejection and respectfully request the withdrawal thereof.

35 USC 112, second paragraph only requires that the claims set forth the subject matter of the invention and that the claims particularly and distinctly point out and distinctly define the metes and bounds of the invention. In the absence of evidence to the contrary, the Examiner is to presume that the subject matter set forth in the claims is the invention for which the Applicants are seeking patent protection.

The claims of the present application recite the use of certain antagonists. Compounds having the claimed activity were known in the art prior to the filing of the original applications upon which this application is based. As discussed above, known techniques can be used to determine whether a compound is a NK_1 antagonist or a $5HT_3$ antagonist.

The Examiner has not pointed to evidence in the specification that Applicants are claiming subject matter that is not regarded as the invention. Further, the Examiner has not specifically pointed

out why the claims are considered to be indefinite, but has only made the assertion "Criteria defining that broad spectrum of medicaments that are useful as NK_1 antagonists, or $5HT_3$ antagonists are not set forth in the specification, thereby failing to provide information defining the instant inventions metes and bounds."

Applicants submit that there is no requirement for Applicants to provide additional criteria thereby narrowing the already defined terms of the claims, in this instance NK_1 receptor antagonists and $5HT_3$ antagonists. Pursuant to MPEP 2173.04 and In re Miller, 441 F.2d 689, 169 USPQ 597 (CCPA 1971), breath of claims is not to be equated with indefiniteness. Applicant's invention is directed to a method of treating emesis with a combination of any NK_1 receptor antagonist and any $5HT_3$ antagonist. As long as the scope of the claimed subject matter is clear and there is no intention to claim subject matter not embraced by the recited claims, then the claims meet the requirements of 35 U.S.C. § 112, second paragraph.

Moreover, it is not necessary to include in the specification that which is already well known in the art. See Hybritech v. Monoclonal Antibodies, Inc., 802 F.2d, 1367, 1384 (Fed. Cir. 1986), which holds that "a patent need not teach, and preferably omits, what is well known in the art."

The Examiner's indefiniteness rejection seems to be based on the enablement requirements. MPEP 2173.04 addresses this issue. "If a claim is too broad because it is not supported by the original description or by an enabling disclosure, a rejection under 35 USC 112, first paragraph would be appropriate." As such, Applicants submit that this indefiniteness rejection is inappropriate and should be withdrawn as Applicants have particularly and distinctly recited the subject matter of the invention.

Acknowledgement of PTO Form 1449

Please provide the undersigned with an initialed PTO Form 1449 acknowledging that the references filed in the Information Disclosure Statement originally dated March 5, 2002 and refiled April 11, 2002 have been considered.

Conclusion

As Applicants have addressed and overcome all rejections in the Office Action, Applicants respectfully request that the rejections be withdrawn and that the claims be allowed.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully

requested to contact Kecia Reynolds (Reg. No. 47,021) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) months extension of time for filing a reply in connection with the present application, and the required fee of $420.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Brown et al., Tachykinin Antagonists, Hakanson, R. and Sundler, F. (Eds.) Elsevier:Amsterdam, pages 305 to 312 (1985);

Bulter, A. et al., Pharmacological Properties of GR38032F, a novel antagonist at 5-HT_3 receptors, *British Journal of Pharmacology*, 94(2), pp. 397-412 (1988).

Bradley et al., "Proposal for the Classification and Nomenclature of Functional Receptors for 5-Hydroxytryptamine," *Neuropharmacology*, Vol. 25, No. 6, pp. 563-576 (1986).

Dutta, A. S.: "*Tachykinin Receptors*". *Comprehensive Medicinal Chemistry*, vol. 3, pp 1001 - 1022. Ed. Emmett, J.C. (1990);

J. Fozard, et al., Blockade of Neuronal Tryptamine Receptors by Metoclopramide, *European Journal of Pharmacology*, vol. 49, pp. 109-112 (1978);

J. Fozard, et al., Blockade of Serotonin Receptors on Autonomic Neurones by (-) Cocaine and Some Related Compounds, *European Journal of Pharmacology*, vol. 59, pp. 195-210 (1979).

U. S. Patent 5,576,317

U.S. Patent 4,695,578

U.S. Patent 4,886,808

U.S. Patent 5,202,333

U.S. Patent 4,906,755

U.S. Patent 5,360,800

GB 2152049A

GB 2100259A

Electronic Orange Book Listings for Ondansetron,

Granisetron, Palonosetron, Dolasetron and Alosetron

Physician's Desk Reference Listing